Development of novel drugs for NG: translational challenges

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Development of novel drugs for *N. gonorrhoeae*: translational challenges

- Considerations on development of new drugs against NG
- Perspectives on Target Product Profile for NG
- Non-clinical activities up to IND
- Beyond IND: Translational PK/PD challenges
Addressing the need for new antibacterials

• **Mission**: Address unmet medical needs by leveraging FabI Inhibitors, a new class of antibiotics
  - **Novel MoA**: Disruption of the bacterial fatty acid biosynthetic pathway preventing bacterial growth
  - Very low potential for spontaneous resistance development and no cross-resistance with other Ab
  - Potent and very narrow spectrum antibiotics with potential for pathogen-specific therapy
  - Low off-target selection pressures and preservation of gut microbiota

• **Most advanced FabI inhibitor**: AFABICIN in the treatment of staphylococcal infections
  - Inactive against all nonstaphylococcal gram-positive and gram-negative pathogens
  - Promising clinical activity seen in ABSSSI - Phase II trial

• **Preclinical Pipeline**:
  - New FabI inhibitor against *N. gonorrhoeae* incl. multi-resistant strains
  - New FabI inhibitor against *A. baumannii* incl. multi-resistant strains

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Considerations on development of new drugs against NG
Development of new antibiotics for NG represents a high risk of failures for developers

1. **Rapid emergence** of *N. gonorrhoeae* resistance or decreased susceptibility\(^1,2\)
   • Consistent problem after introduction of any new therapeutic antimicrobial for gonorrhea

2. **Limited knowledge** regarding the pharmacokinetics and pharmacodynamics of the available antimicrobials in the treatment of gonorrhea, particularly **extragenital sites**\(^1,2\)
   • Pharyngeal infections are frequently asymptomatic but play a major role in resistance development\(^3\)

3. **Multiple dose regimens** for gonorrhea might be required for difficult-to-treat extragenital infections\(^1,2\)
   • However, single dose Directly Observed Therapy is preferred to ensure medications are delivered\(^1\)

4. **Changes in the treatment guidelines** for NG infections are frequent and may be different across countries
   • Regulatory challenge for ongoing clinical programs

5. **Lack of knowledge** about **fundamental aspects on the pathogenesis/pathophysiology**
   • Debate on relevance of intracellular vs extracellular antibacterial activity for selection of drug candidates\(^2\)

Perspectives on TPP for NG
## Perspectives on TPP for NG

### Selected points for discussion

<table>
<thead>
<tr>
<th></th>
<th>Acceptable TPP</th>
<th>Ideal TPP</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Treatment of Uncomplicated Urogenital <em>Neisseria gonorrhoeae</em> infections (susceptible and MDR)</td>
<td>First line treatment of Uncomplicated Urogenital, Ano-rectal and Oro-pharyngeal <em>Neisseria gonorrhoeae</em> infections (susceptible and MDR)</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Adults</td>
<td>Adults, adolescents</td>
</tr>
<tr>
<td><strong>Clinical Efficacy</strong></td>
<td>Non-inferiority to current SoC</td>
<td>Non-inferiority to current SoC</td>
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<tr>
<td><strong>Safety and Tolerability</strong></td>
<td>Minimal outpatient monitoring required post treatment</td>
<td>No patient monitoring required post treatment</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral or IM</td>
<td>Oral and IM</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Single Dose or Multiple Doses</td>
<td>One or two doses</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>3-5 days</td>
<td>1 day</td>
</tr>
<tr>
<td><strong>In vitro activity</strong></td>
<td>Bactericidal/static, limited cross-resistance, low potential for emergence of cross-resistance</td>
<td>Bactericidal, intracellular activity, no cross-resistance, low potential for emergence of cross-resistance</td>
</tr>
<tr>
<td><strong>Activity against extended spectrum cephalosporins and macrolide resistant strains</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drug Drug interaction profile</strong></td>
<td>Minimal relevant DDIs including HIV and other STD treatments</td>
<td>No relevant DDIs including HIV and other STD treatments</td>
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</table>
Non-clinical activities up to IND
Overview

• Standard, well-defined package as per ICH guidelines

Key points

• Duration of GLP toxicity studies varies across regions:
  • FDA may accept short duration studies, at least equivalent to intended treatment in FIH: quicker path to FIH, lower API amounts required
  • However, requirements from other regulatory bodies (e.g. EU) ask for 2 weeks treatment

➢ Conducting only 2-week studies to support global development - most cost-effective option
Overview

• Standard NG susceptibility testing and culture are performed on agar media
• However, a number of conventional assays suggested by the guidances (MBC, killing curves, PAE) can only be performed in liquid cultures

Key points

• Several liquid media support NG growth, however the assay settings (e.g. starting inoculum, growth kinetics) impact the model performance
  • Challenges in evaluating the comparative performance of different compounds
• Alternative approach of using surrogate organisms is not satisfactory
  • MoA / killing kinetics may not be identical across species

➤ Data from liquid cultures should be considered exploratory and not essential
Overview

- Non-clinical NG programs mostly relied on surrogate models (e.g. SA neutropenic mouse thigh) for PK/PD\(^1,2\)
- Emerging evidence supports the use of the mouse vaginal NG infection model\(^3\) as a PK/PD tool\(^4\)
  - Promising model but has not been used as prospective translational PK/PD tool

Key points

- Recent internal data on a number of compounds suggest that robust PK/PD can be generated using the mouse vaginal NG infection model
  - Reproducible and quantitative dose-response
  - Identification of PK/PD index and magnitude associated with various bacterial endpoints

Robust data generated with this model should be considered appropriate for regulatory purposes

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\(^1\) Scangarella-Oman et al, Antimicrob Agents Chemother 2018
\(^2\) Bradford et al, ACS Infect Dis 2020
\(^3\) Jerse et al, Front. Microbiol. 2011
\(^4\) Theuretzbacher et al, Clin Microbiol Infect 2020
Beyond IND

Translational PK/PD challenges
Potential approaches to predict antibacterial activity in extragenital infection sites

Overview

• Relevant animal models for anorectal and pharyngeal infections are not (yet) available\(^1\)

Key attributes to explore in the absence of models

• Appropriate physicochemical characteristics (e.g. cell permeability) during Lead Optimization
• Tissue distribution and penetration in infection sites (e.g. MALDI-MS, PBPK)
• Intracellular activity (currently only urethral/endometrial epithelial cell lines, PMNs models)
• Impact of treatment duration, despite limitations of current methodologies

➢ Ongoing research and new developments are paramount to bridge the PK/PD gap for NG

\(^1\) Conolly \textit{et al}., Antimicrob. Agents Chemother. 2019
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## PK/PD for urogenital NG infections

### Translational PK/PD challenges

<table>
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<tr>
<th>Approach*</th>
<th>Advantages</th>
<th>Drawbacks</th>
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| Vaginal NG model | • Target pathogen  
• Increasing evidence supporting use for PK/PD | • Bacterial endpoints associated with clinical efficacy are not known  
• Different adhesion/invasion pathways vs human |
| Surrogate pathogen | • Approach already used for several programs  
• Supports efficacy in urogenital infections (stasis / 1 log kill) | • Intrinsic risk : different bacterial species  
• May not be feasible for narrow-spectrum antibiotics |
| Hollow fiber model | • Well suited to identify PK/PD driver  
• Uses target pathogen | • Bacterial endpoints associated with clinical efficacy are not known  
• No interplay with living organism |

* Not an exhaustive list